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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,592	08/17/2005	Ronald Rodriguez	58799(71699)	9269

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EXAMINER

WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
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1635

MAIL DATE	DELIVERY MODE
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11/14/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,592	RODRIGUEZ ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 August 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 16,17,19,20,22 and 34-38 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 16,17,19,20,22,34-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>8/25/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 8/25/08 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 17, 19, 20, 22 and 33-38 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing a cell in vivo using direct delivery of the adenovirus to the cell and a method of killing a cell in vitro, does not reasonably provide enablement for a method of killing a cell in vivo using a genus of administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or

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guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention reads on a method of killing a cell that is sensitive to DT-A or PEA. The cell can be a cancer cell. The cell can be either in vitro or in vivo. The claimed invention embraces using a genus of administrations routes to a cell in vivo.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (United States v. Technologies Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather a conclusion reached by many factors. These factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in In Re Wands (see above).

The invention lies in the field of gene therapy.

At the time the application was filed, gene therapy was considered to be unpredictable due to significant problems in several areas. The state of the art for gene therapy is exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

- 1) The type of vector and amount of DNA constructs to be administered,
- 2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be

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successful (page 238, columns 1 and 2). Thus, the state of the art of gene therapy is considered highly unpredictable.

In further view of the doubts expressed above by Anderson and Verma, the state of the art at the time the application was filed and currently for cancer gene therapy as discussed by Vile et al., (*Gene Therapy*, Vol. 7, pp. 2-8, 2000) and McNeish et al (*Gene Therapy* 2004, Vol. 7, 1-7). Vile teaches:

The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. None the less, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious contender unless it has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).

Vile further discusses:

A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for the treatment of cancer requires not only that the

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vectors be targeted (to infect only tumor cells) but also that they be protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).

Applicants provide no working examples of the claimed invention. Applicants do produce a packaging cell line for producing an adenovirus expressing A subunit of Diphtheria Toxin (DT-A) or Pseudomonas Exotoxin A (PEA). However, the relevance of this data to killing cells in vivo is unclear at best because neither the applicants nor the prior art provide a correlation or nexus between the results obtained by applicants with practicing the claimed gene therapy method. However, the prior art (Maxwell et al., Cancer Research, 1986, cited on PTO-1449) teaches that DT-A and PEA can be used to kill tumor cells in vivo. Thus, the skilled artisan would reasonably determine that the toxins could be used to kill cells sensitive to PEA or DT-A in a subject.

Furthermore, with respect to the claimed methods reading on a cell in vivo, it would take one skilled in the art an undue amount of experimentation to determine what route of administration (e.g. intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) other than direct administration and/or systemic administration of an adenovirus would result in a therapeutic response using a vector embraced in the claims. The applicants teach IJ or IP were suitable administration routes for delivering an adenovirus comprising the claimed nucleic acid into the liver of mice infected with

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HCV. The skilled artisan cannot reasonably extrapolate from the results using an adenovirus to a genus of vectors because each vector has a different mechanism and tropism. The state of the art for the route of administration for gene therapy as exemplified by Verma (*supra*) and Vile (*supra*), indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). At the time of filing, Ye et al. () teach that systemic delivery of an adenovirus results in adenovirus being sequestered in the liver (Human Gene Therapy, 11: 621-627, 2000) and Einfeld et al. (Current Opinions in Molecular Therapeutics 4: 444-451, 2002). In view of the art of record, it is not apparent to one skilled in the art how to reasonably extrapolate from direct administration to a genus of administration routes to generate a therapeutic response in a genus of subjects with HCV.

In conclusion, the instant specification and claims coupled with the art of record, at the time the invention, was made only provide enablement for an *in vitro* method of suppressing growth of a cancer cell and an *in vivo* method of suppressing growth of a cancer cell in a subject comprising direct administration to the cancer cell and not for the full scope of the claimed invention. Given that gene therapy wherein a genus of nucleic acids was employed to correct a disease or a medical condition in a genus of mammals was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy method for treating a genus of cancers in a

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genus of mammals, one skilled in the art would have to engage in a large quantity of undue experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Applicant's arguments filed 8/25/08 have been fully considered but they are not persuasive.

In response to applicant's argument that a genus of administration routes for use in the claimed invention is enabled (see specification) in view of the art of record, the argument is not found persuasive because the art of record teaches the problems of delivering a replication defective adenovirus to cells in vivo and the mere contemplation in the specification does not teach the skilled artisan how to practice the full scope of the claimed invention without an undue amount of experimentation. In addition, Applicants provide no working example of the claimed invention. While it is acknowledged that applicant need not disclosed a working example, it is only a rule of supplementation, not a substitute for basic enabling disclosure. See *Automotive Technologies International, Inc. v. BMW of North America, Inc., et al.* (Fed. Cir. 2007) Federal Circuits, Fed. Cir. (September 06, 2007) Docket number: 06-1013.

In response to applicant's argument that a post-filing reference (Castro et al. 2007) supports the applicant's argument that the claimed inventions are enable, the argument is not found persuasive because the reference teaches intratumoral (direct) administration of an adenovirus to tumor cells, which would support the scope of enablement rejection of record. The reference does not support, at the time of filing,

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that the specification was enabled for using a genus of administration routes without an undue amount of experimentation. See Ye al. (supra).

In response to applicant's argument that Verma, McNeish, and Vile describe general concepts regarding gene therapy, and to date there are dozens of clinical trials in the U.S. and many more around the world that involve gene therapy and while failures may occur, it is important to consider the success that have occurred in the field of gene therapy, the argument is not found persuasive because McNeish and Vile are directed to cancer gene therapy and do involve concepts that are considered problems for the skilled artisan to overcome with cancer gene therapy before the skilled artisan can practice the a genus of administration routes. For example, at the time of filing, Vile states, "In truth, no such systemically targeted vectors exist yet (page 4)." See also Ye et al. (supra).

With respect to applicant's argument about the number of gene therapy trials, the argument is not found persuasive because while it is acknowledged that other types of gene therapies have been cited in the art for treating a particular disease or genetic disorder using distinct material(s) and method step(s), the art of record teaches that one skilled in the art can not reasonably extrapolate from one type of gene therapy or vector to another type of gene therapy or vector without an undue amount of experimentation.

In response to applicant's argument that Blaese et al. (Science 1995) teaches ex vivo gene therapy for treating ADA using genetically modified cells comprising a retrovirus, the argument is not found persuasive because ex vivo gene therapy for ADA is considered enabled, however, the rejection is based on using a genus of

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administrations routes for cells in vivo. Blaese et al. do not address this problem. In addition, retroviral vectors are different material than adenoviral vectors.

In response to applicant's argument that Crystal (1995) Roth et al. (Nature Medicine, 1996), Khuri et al. (Nature Medicine, 2000), Cavazzana-Calvo et al. (Science, 2000 and Kay et al. (Nature Genetics, 2000) support the enablement of the claimed invention, the argument is not found persuasive because none of the articles teaches cancer gene therapy using replication adenoviral vectors. The closest art cited is Khuri et al. which is directed to replication competent adenoviruses not replication defective adenoviruses. In addition, Khuri et al. teach using intratumoral delivery of the adenovirus (page 883).

With respect to the general statement (most studies have shown that genes can be transferred to human whether the strategy is ex vivo or in vivo and that all vector types function as intended) by Crystal, the statement does not teach the skilled artisan how reasonably extrapolate from a general concept to using a genus of administration routes in the claimed method without an undue amount of experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16, 17, 19, 20, 22, and 34-38 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted

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elements are: an adenoviral vector comprising a promoter operably linked to a nucleic acid encoding DT-A or PEA. While the claims define a cell line capable of producing the adenoviral vector, the claims do not include the adenoviral vector to complete the preamble of the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number 571-272-0764. The examiner can normally be reached on from 6:30 to 4:00 (Eastern Standard Time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Brian Whiteman/

Primary Examiner, Art Unit 1635